192. The method of **Claim 191** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.

E12 Conclude

193. The method of **Claim 186**, wherein the GLP-1 molecule is administered as an aerosol.

194. The method of **Claim 193,** wherein the GLP-1 molecule is delivered from an inhalation device is selected from the group consisting of a nebulizer, a metered-dose inhaler, and a sprayer.

Remarks

On October 7, 2002, a telephonic interviews was held between Gregory A. Cox and Examiner David Lukton. The Examiner is thanked for granting the telephonic interview and for his helpful comments. It was agreed that the Examiner would consider an amendment whereby the claims recited the endpoint of normalizing blood glucose in response to hyperglycemic conditions by the process of administering an effective dose to the lungs of a patient. In addition, it was agreed that the Examiner would reconsider the claims reciting the word "about" as not being indefinite. Finally, it was agreed that the Examiner would consider a genus of GLP-1 compounds that are structurally defined by the formulas in the specification.

In this response, Applicants have canceled claims 122, 133, 141, 143, 154, 162, 164, 173, 181, and 183. Applicants have amended claims 123, 134, 142, 144, 155, 163, 165, 168, 174, 180, and 182. Support for independent claims 123, 144, and 165 can be found throughout the specification and in particular on page 5, lines 19 to 22, page 7 lines 5 to 12, and page 14, lines 15 to 18. More particular, support for claim 123 can be found on page 9, lines 1 to 17, support for claim 144 and 165 can be found on page 9, line 18 to page 10, line 28. Claims 134, 142, 155, 163, 174, and 182 are amended to change their dependencies following canceled claims. Claims 168 and 180 are amended to change their dependencies. New Claims 184 to 194 have been added. Support for these claims can be found on page 10, line 29 to page 11 line 8.

REJECTION UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner rejected Claims 122-183 under 35 U.S.C. §112 first paragraph as containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner suggests that the claimed invention includes the possibility of raising blood glucose. The Examiner states that raising blood glucose is not enabled. Applicants are not contending that administration of a GLP-1 compound to the lungs of a patient raises blood glucose. Normalizing blood glucose by administering a GLP-1 compound is clear to a person skilled in the art. GLP-1 is well known as a *glucose dependent* stimulator of insulin secretion. It could not be contemplated that administering a GLP-1 compound to the lungs of a patient in need of normalizing their blood glucose would raise blood glucose if they were suffering from hypoglycemia. In fact, the great potential of a future GLP-1 compound as an approved drug is that it is one of the most potent insulin-secretagogues-identified-and it-is-glucose dependent.- (See Deacon et al. *Diabetologia* 41, 271,1998, cited by the Examiner in Paper No. 6). Therefore, in a hypoglycemic state, a GLP-1 compound would have no effect on insulin secretion. The Examiner even mentions GLP-1 stimulates insulin release. Insulin is well know to lower blood glucose; it does not raise blood glucose. However, to put the claims in allowable format, Applicants have amended independent claims 123, 144, and 165 to include normalizing blood glucose in a patient suffering from hyperglycemia, thus avoiding the Examiner's interpretation that GLP-1 could raise blood glucose in a hypoglycemic patient. Applicants respectfully request withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

The Examiner rejected Claims 122-183 under 35 U.S.C. §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 122 has been canceled. Therefore, rejection regarding "dipetidyl" is now moot.

The claims were rejected as being indefinite as to the process steps and endpoint. The Examiner offers that the claims recite that the GLP-1 compounds are administered "for a time and under conditions to mitigate hyperglycemia," or, "for a time and under conditions effective to lower plasma glucose." This language is implicit in Applicants' language of normalizing blood glucose by administering to a patient in need of normalizing blood glucose

a GLP-1 compound. As stated above and in the Deacon et al. reference, GLP-1 is glucose dependent. If a patient has abnormally high blood glucose levels, then administration of a GLP-1 compound would result in normalizing their blood glucose. Thus, a method of normalizing blood glucose necessarily entails for a time and under conditions to mitigate hyperglycemia or lower blood glucose. Applicants' specification states, "GLP-1 treatment offers a way to normalize blood glucose only in response to hyperglycemic conditions without the threat of hypoglycemia." (See page 5, lines 19-22).

Further, normalization of blood glucose will occur after a period of time and under conditions when the peptide is circulating at therapeutic levels in the serum of a patient. The patient's desired endpoint is to normalize their blood glucose levels. The specification states, "GLP-1 related compounds described above are administered by inhalation in a dose effective manner to introduce circulating therapeutic levels which results in reducing abnormally high blood glucose levels." (See page 14, lines 15 to 18). Thus, the ordinary skilled person would know that the process the patient would go through would be to administer an effective dose of a GLP-1 compound for a time and under conditions to achieve the desired endpoint of normalized blood glucose. However, to put the claims in allowable format, Applicants have amended independent claims 123, 144, and 165 to include the process and endpoint of normalizing blood glucose in a patient suffering from hyperglycemia by administering an effective dose, thus providing the process steps and endpoint the Examiner requested. Applicants respectfully request withdrawal of this rejection.

Claims 136-139, 171, 172, and 176-179 were rejected for reciting the phrase "about" in reference to a range. Applicants continue to disagree with the merits of this type of rejection. Applicants rely on consistency at the Patent Office. In the previous rejection, the Examiner rejected Applicants language of "less than about" as indefinite as to which term dominates, the "about", or the "less than." Applicants offered that since 1996 more than 12,000 U.S. patents have issued with "less than about" language in the claim, and more than 15,000 U.S. patents have issued with "at least about" language in the claim. Now, the Examiner is rejecting the word "about" in reference to a range. This rejection is inconsistent with the law and the practice of the Patent Office. The MPEP states that "about" is definite unless there is close prior art. (MPEP § 2173.05(b)(A)). (*See also Ex parte Eastwood,* 163 USPQ 303 (Bd. App. 1968) and *W.L. Gore v. Garlock, Inc.,* 721 F.2d 1540 (Fed. Cir. 1983)). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 133, 141, 173, and 181 have been canceled without prejudice to further prosecute this claim in a continuation application. Therefore, the Examiner's rejection of the claims being indefinite for reciting the phrase "capable of depositing" is now moot.

Claims 143 and 164 have been canceled without prejudice to further prosecute this claim in a continuation application. Therefore, the Examiner's rejection for improper dependency of the claims is now moot.

REJECTION UNDER 35 U.S.C. § 103

Applicants have canceled claim 122 in this application without prejudice to further prosecute this claim in a continuation application. Therefore the obviousness rejection is now moot.

SUMMARY AND CONCLUSION

Applicants respectfully assert that the application is now in condition for allowance. Applicants have enabled their invention as claimed. The claims are definite and particularly point out and distinctly claim the subject matter being sought. The Examiner's case of obviousness is now moot. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,

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Attachment A

Marked-up copy of amendments as required by 37 C.F.R. §1.121(b)(iii)

In the Claims:

123. (amended) A method of normalizing blood glucose comprising administering an effective dose of a glucagon-like peptide-1 (GLP-1) molecule to the lungs of a patient suffering from hyperglycemia, wherein the GLP-1 molecule has an amino acid sequence of a formula:

R_1-X-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Y-Gly-Gln-Ala-Ala-Lys-Z-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-R_2

(SEQ ID NO:1)

wherein:

R_1 is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly; and

R_2 is selected from the group consisting of NH_2, and Gly-OH.

134. (amended) The method of **Claim 128,** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.

142. (amended) The method of **Claim 140,** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, [a dry powder inhaler,] and a sprayer.

144. (amended) A method of normalizing blood glucose comprising administering an effective dose of a GLP-1 molecule to the lungs of a patient suffering from hyperglycemia, wherein the GLP-1 molecule is GLP-1(7-34), GLP-1(7-35), GLP-1(7-36), or GLP-1(7-37), or the amide forms thereof, comprising at least one modification selected from the group consisting of:

(a) substitution of a glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, arginine, or D-lysine for lysine at position 26 and/or position 34 or substitution of a glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, lysine, or a D-arginine for arginine at position 36;

~~(b) substitution of an oxidation-resistant amino acid for tryptophan at position 31;~~

(c) substitution according to at least one of:

Y for V at position 16;

K for S at position 18;

D for E at position 21;

S for G at position 22;

R for Q at position 23;

R for A at position 24; and

Q for K at position 26;

(d) substitution comprising at least one of:

glycine, serine, or cysteine for alanine at position 8;

aspartic acid, glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine for glutamic acid at position 9;

serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine for glycine at position 10; and

glutamic acid for aspartic acid at position 15; and

(e) substitution glycine, serine, cysteine, threonine, asparagine, glutamine,

tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine or the D or N-acylated or alkylated form of histidine for histidine at position 7.

155. (amended) The method of **Claim 149,** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.

163. (amended) The method of **Claim 161,** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, [a dry powder inhaler,] and a sprayer.

165. (amended) A method of normalizing blood glucose comprising administering an effective dose of a GLP-1 molecule to the lungs of a patient suffering from hyperglycemia, wherein the GLP-1 molecule is a GLP-1 derivative prepared by the process of acylating a GLP-1 analog selected from the group consisting of GLP-1(7-34), GLP-1(7-35), GLP-1(7-36), and GLP-1(7-37), or the amide forms thereof, comprising at least one modification selected from the group consisting of:

(a) substitution of a glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, arginine, or D-lysine for lysine at position 26 and/or position 34 or substitution of a glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, phenylalanine, lysine, or a D-arginine for arginine at position 36;

(b) substitution of an oxidation-resistant amino acid for tryptophan at position 31;

(c) substitution according to at least one of:

Y for V at position 16;

K for S at position 18;

D for E at position 21;

S for G at position 22;

R for Q at position 23;

R for A at position 24; and

Q for K at position 26;

(d) substitution comprising at least one of:

glycine, serine, or cysteine for alanine at position 8;

aspartic acid, glycine, serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine for glutamic acid at position 9;

serine, cysteine, threonine, asparagine, glutamine, tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine for glycine at position 10; and

glutamic acid for aspartic acid at position 15; and

~~(e) substitution glycine, serine, cysteine, threonine, asparagine, glutamine,~~ tyrosine, alanine, valine, isoleucine, leucine, methionine, or phenylalanine or the D or N-acylated or alkylated form of histidine for histidine at position 7.

168. (amended) The method of **Claim 167** wherein the GLP-1 molecule is in the form of a dry powder.

174. (amended) The method of **Claim 168** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.

180. (amended) The method of **Claim 167**, wherein the GLP-1 molecule is administered as an aerosol.

182. (amended) The method of **Claim 173**, wherein the GLP-1 molecule is delivered from an inhalation device is selected from the group consisting of a nebulizer, a metered-dose inhaler, [a dry powder inhaler,] and a sprayer.